

Neuroprotective and plasticity promoting effects of repetitive transcranial magnetic stimulation (rTMS): A role for microglia

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ARTICLE INFO

Keywords:

repetitive transcranial magnetic stimulation
microglia
Synaptic plasticity
Neuroprotection

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique used to modulate neocortical excitability, with expanding applications in neurological and psychiatric disorders. However, the cellular and molecular mechanisms underlying its effects, particularly the role of microglia –the resident immune cells of the central nervous system– remain poorly understood. This review synthesizes recent findings on how different rTMS protocols influence microglial function under physiological conditions and in disease models. Emerging evidence indicates that rTMS modulates microglial activation, promoting neuroprotective and plasticity-enhancing processes not only in models of brain disorders, such as Alzheimer's and Parkinson's disease, but also in healthy neural circuits. While much of the current research has focused on the inflammatory profile of microglia, critical aspects such as activity-dependent synaptic remodeling, phagocytic activity, and process motility remain underexplored. Given the substantial heterogeneity of microglial responses across brain regions, age, and sex, as well as their differential roles in health and disease, a deeper understanding of their involvement in rTMS-induced plasticity is essential. Future studies should integrate selective microglial manipulation and advanced structural, functional, and molecular profiling techniques to clarify their causal involvement. Addressing these gaps will be pivotal in optimizing rTMS protocols and maximizing its therapeutic potential across a spectrum of neurological and neuropsychiatric conditions.

1. Background

Repetitive transcranial magnetic stimulation (rTMS) is a neurophysiological technique pioneered by Anthony Barker and his team in 1985 [1,2]. The method uses a time-varying magnetic field generated by a coil placed over the subject's scalp. This magnetic field penetrates the intact skin, skull, and meninges, inducing localized electric fields in the neocortex [3]. rTMS can be administered using various frequency patterns, each exerting specific neuromodulatory effects. Low-frequency rTMS (<5 Hz) has been shown to reduce cortical excitability, a mechanism often attributed to the induction of long-term depression (LTD) of excitatory neurotransmission. In contrast, high-frequency (HF) rTMS (≥5 Hz) facilitates long-term potentiation (LTP), strengthening excitatory synaptic connections [4,5]. Theta-burst stimulation (TBS) is a variant of rTMS that delivers bursts of three pulses at 50 Hz, repeated

every 200 ms (5 Hz). TBS is applied in two main forms: intermittent TBS (iTBS), approved by the US Food and Drug Administration (FDA) for the treatment of depression, delivers 2-s bursts every 10 s for a total of 600 pulses and increases neural excitability, inducing LTP-like plasticity in targeted circuits [6]. Continuous TBS (cTBS) administers the same 600 pulses over an uninterrupted 40-s period, reducing neural excitability [7]. More recently, accelerated iTBS protocols with up to 1800 pulses have been successfully implemented in clinical settings [8]. However, these findings are based primarily on indirect system-level measures, such as changes in muscle-evoked potentials during motor cortex stimulation, and direct experimental evidence for rTMS-induced LTP or LTD in the human neocortex is still lacking.

The ability of rTMS to selectively modulate brain regions, combined with its favorable safety profile and lower risk compared to invasive intracranial electrical stimulation, has led to its widespread use in

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<https://doi.org/10.1016/j.brs.2025.03.012>

Received 6 January 2025; Received in revised form 10 March 2025; Accepted 17 March 2025

Available online 19 March 2025

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neuroscience research with healthy participants and as a therapeutic tool for various brain disorders [9,10]. Over the past decades, rTMS has been particularly effective in treating psychiatric disorders, with notable success in major depressive disorder and obsessive-compulsive disorder [11–13]. Additionally, rTMS has shown promise as a potential therapeutic intervention for neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), as well as for multiple sclerosis, neuropathic pain, and ischemic stroke [14–16]. Yet, current applications (both in research and clinical practice) are based on heuristics and informed by indirect systems-level measurements or extrapolation from findings made in animal studies.

Experimental evidence in rodents has provided insights into the neural mechanisms of rTMS [17,18]. Murphy et al. (2016) demonstrated that single-pulse TMS inhibits neocortical dendritic Ca^{2+} activity evoked by tactile stimulation in rats [19]. This inhibitory effect was prevented by blocking both excitatory AMPA receptor-mediated transmission in upper cortical layers and $GABA_B$ receptors on pyramidal dendrites, suggesting an upstream recruitment of dendrite-targeting inhibitory neurons in the neocortex. In feline studies, HF-rTMS was shown to weaken inhibition, driving changes in cortical excitability [20] and remodeling visual cortical maps [21]. These findings highlight the role of inhibitory modulation in rTMS-induced plasticity. *In vitro* research using mouse entorhinal-hippocampal slice cultures has revealed that 10 Hz rTMS enhances the functional and structural properties of excitatory synapses through postsynaptic changes. These changes are mediated by NMDA receptor-dependent accumulation of GluA1-containing AMPA receptors [22]. Concurrently, 10 Hz rTMS decreases GABAergic synaptic strength through structural modifications of dendritic inhibitory postsynapses [23]. These studies contribute to our understanding of the complex interplay between excitatory and inhibitory mechanisms in rTMS-induced neural plasticity across various animal models and experimental paradigms. Although the plasticity promoting effects of rTMS are increasingly recognized, many of the cellular and molecular mechanisms underlying its impact on the brain remain poorly understood. Notably, the role of non-neuronal cells in the central nervous system, which are critical for supporting and regulating neuronal activity and plasticity, has been largely overlooked in rTMS research. Given that microglia play a key role in maintaining brain homeostasis and mediating neuroinflammatory responses [24], understanding their involvement in rTMS-induced effects could offer valuable insights for optimizing this therapeutic approach in treating various neurological conditions.

2. Microglia: important player in neuronal activity modulation

Microglia, the primary resident immune cells of the central nervous system (Fig. 1A), are essential in conducting immune surveillance, maintaining neuronal homeostasis, and regulating neural networks [25, 26]. A primary mechanism through which microglia control and maintain proper neuronal activity is synaptic remodeling, a dynamic process involving the formation, elimination, and modification of synapses. This microglial-mediated synaptic remodeling is essential for proper brain development, plasticity, and the maintenance of neural circuit integrity [27].

During development, microglia play a crucial role in refining neural circuits by actively pruning synapses through engulfment and phagocytosis of synaptic elements [28–32]. Furthermore, microglia identify synapses for pruning through signals such as complement system proteins C1q and C3, which tag synapses for elimination [33–35].

Beyond pruning, microglia modulate synaptic formation, strength, and plasticity through direct contact with synapses, phagocytosis-mediated synaptic pruning [36,37], and the release of signaling molecules such as cytokines, chemokines, and growth factors [38–41]. Brain-Derived Neurotrophic Factor (BDNF) is a key regulator of experience-dependent synaptic plasticity [42]. While neurons are a major source of BDNF in the healthy brain, particularly for synaptic plasticity, microglia-derived BDNF is increasingly recognized as a crucial modulator of neural function, especially in disease states and developmental periods [43,44]. Recent research by Komori et al. (2024) revealed that microglial BDNF is overexpressed in the medial prefrontal cortex (mPFC) of socially isolated juvenile mice, leading to alterations in normal synaptic function [43]. Earlier evidence for the role of microglial BDNF in synaptic remodeling associated with learning and memory was provided by Parkhurst et al. (2013). Their study demonstrated that genetic depletion of BDNF specifically from microglia recapitulates the experience-dependent synaptic plasticity impairments observed when microglia are entirely depleted [45]. Although BDNF is widely implicated in rTMS-induced plasticity [46,47], direct experimental evidence supporting BDNF- and TrkB-mediated signaling in rTMS-induced synaptic plasticity remains limited [48].

The ability of microglia to modulate neuronal activity was initially demonstrated *in vitro* by incubating primary neuronal cultures or acute brain slices with microglia-conditioned medium. These experiments identified multiple microglia-released signaling molecules, including neurotransmitters, extracellular matrix proteins, micro-vesicles and cytokines, that collectively regulate various aspects of synaptic function and plasticity [49–54]. Indeed, recent studies have demonstrated that

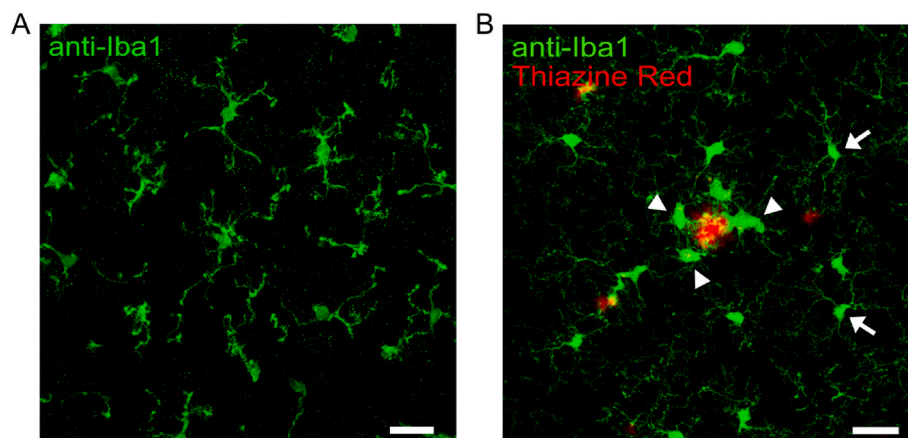


Fig. 1. Microglia in health and disease. **A** Confocal image of human neocortical microglia visualized by anti-Iba1 immunolabeling (green). **B** Mouse neocortical microglia in 5xFAD transgenic mouse brain tissue. Microglia (green) were immunolabeled with anti-Iba1 antibody while $A\beta$ plaques (red) were visualized using Thiazine Red staining. White arrows indicate non-reactive, ramified microglia distant from plaques. White arrowheads highlight reactive, amoeboid-shaped microglia associated with $A\beta$ plaques, illustrating their morphological transformation in response to pathology. Scale bar: 20 μ m.

microglia may serve as gatekeepers of synaptic change and stability, by mediating homeostatic synaptic plasticity depending on their activation state [40]. In response to aberrant synaptic activity, microglia play a crucial role in restoring physiological neuronal function, thereby protecting the brain from excessive activation in both health and disease states [55–59].

While microglia continually survey their environment with motile processes under physiological conditions, their dysfunction is implicated in various neurological and psychiatric disorders, including AD, autism spectrum disorders, and schizophrenia. In these pathological states, microglia may engage in aberrant synaptic plasticity and pruning [60, 61], contribute to the spread of internalized amyloid-β (Aβ) material [62,63], or fail to clear synaptic debris effectively, thereby exacerbating disease progression. Moreover, in many neurodegenerative diseases, microglia can become chronically reactive, producing neurotoxic concentrations of cytokine that further aggravate the disease course [64, 65]. This reactive state is reflected in their transition from a highly ramified morphology to a more compact, amoeboid shape (Fig. 1B), indicative of enhanced activation and inflammatory signaling.

Given their critical involvement in neurodegenerative and neuropsychiatric disorders, modulating microglial function presents a promising therapeutic avenue. In this context, rTMS is emerging as a potential strategy to influence microglial activity, suggesting that these cells serve as both targets and key mediators of rTMS-induced plasticity, neuroprotection, and therapeutic outcomes. Findings from *in vitro* and *in vivo* studies highlight how these interactions contribute to the therapeutic benefits of rTMS across various neuropsychiatric disorders.

3. Role of microglia in rTMS-induced synaptic plasticity and neuroprotection

A recent study by Eichler et al. (2023) provided direct experimental evidence for the role of microglia in synaptic plasticity induced by 10 Hz rTMS. Using mouse organotypic brain slice cultures, 10 Hz electromagnetic stimulation (900 pulses) triggered the activity-dependent release of cytokines, including tumor necrosis factor α (TNFα) and interleukin 6 (IL6), from microglia. This increase in plasticity-promoting cytokines was not observed when neuronal activity was blocked with the

sodium channel inhibitor tetrodotoxin and absent in microglia-depleted slice cultures, suggesting a direct effect of electric fields on microglia-neuron interactions [38]. Remarkably, the addition of recombinant TNFα and IL6 during stimulation, rescued 10 Hz repetitive magnetic stimulation-induced synaptic plasticity in microglia-depleted tissue cultures. In line with these findings, *in vivo* microglial depletion abolished synaptic plasticity in layer II/III pyramidal neurons of the mouse mPFC exposed to 10 Hz rTMS (Fig. 2A; [38]). These data highlight the essential role of microglia in rTMS-induced synaptic plasticity. Interestingly, despite their critical involvement, microglial morphology and dynamic surveillance behavior remained unchanged following a single 10 Hz intervention [38]. While subtle changes in microglia processes and synapse interactions cannot be ruled out, and their response to pathological stimuli remains untested, these findings suggest that microglia mediate acute rTMS effects primarily through the release of soluble factors rather than structural remodeling.

Research on rTMS and microglia under healthy conditions remains limited. Zorzo et al. (2019) investigated the effects of three days of HF-rTMS (100 Hz; 3000 pulses delivered each minute) on young rats, focusing on neuronal metabolism, activation, and glial responses [66]. Their immunohistochemical analysis revealed no significant differences in microglial density or activation across various cortical and hippocampal sub-regions post-rTMS [66]. Similarly, Liebetanz et al. (2003) applied LF-rTMS (1 Hz; 1000 pulses) to rats for five consecutive days. They observed no changes in microglial density, expression of reactive markers, or phagocytic properties 48 h after the last TMS session [67].

These studies suggest that under physiological conditions, microglia play a crucial role in mediating rTMS-induced neuronal plasticity without adopting a pro-inflammatory phenotype or eliciting neuroinflammation. Moreover, rTMS does not induce significant morphological alterations in microglia, emphasizing their subtle yet essential role in mediating rTMS effects in the healthy brain.

4. Microglia-mediated anti-inflammatory effects of rTMS in pathological conditions

The best documented effect of rTMS on microglia is its anti-inflammatory action, particularly in conditions characterized by

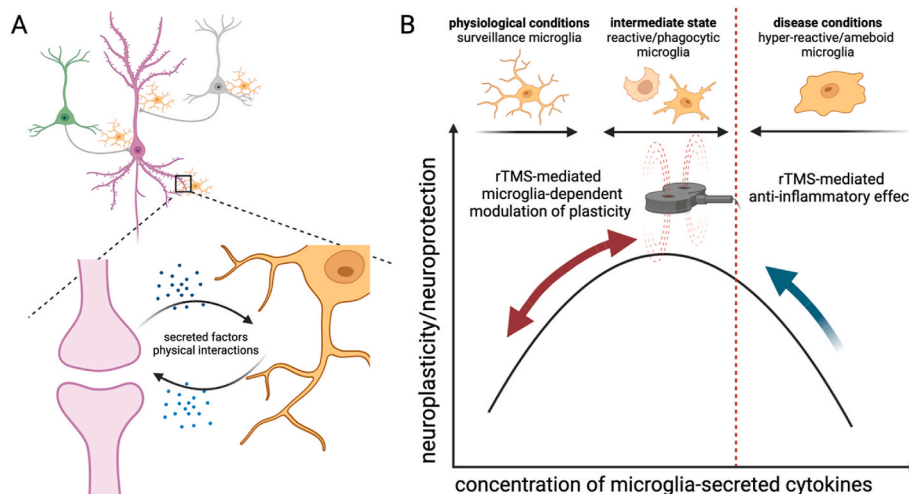


Fig. 2. Impact of rTMS on microglia-mediated synaptic plasticity and neuroprotection. **A** The precise mechanisms by which rTMS influences neural plasticity and the potential role of microglia in mediating input-specific excitatory and inhibitory synaptic plasticity, warrant further investigation. Recent experimental evidence from rodent brain tissue suggests that rTMS-induced neuronal activity stimulates the secretion of plasticity-enhancing cytokines from microglia. **B** Signaling pathways that are active under disease conditions also regulate the ability of neurons to express plasticity under physiological conditions. The effects of microglia-secreted cytokines on synaptic plasticity can depend on factors such as concentration and spatio-temporal exposure. However, the impact of distinct microglia states on the ability of neurons to express plasticity remains poorly characterized, creating a significant gap in our understanding of how these immune responses influence neural circuit function. Emerging evidence suggests that rTMS may modulate the complex interplay between microglia and neurons, thereby promoting and regulating neuroplasticity (created with BioRender.com).

microgliosis—the transformation of resting microglia into an activated state, marked by morphological changes, increased proliferation, and heightened immune responses. By modulating inflammatory signaling through a yet-to-be-identified mechanism, rTMS can help preserve neuronal function and viability. Below, we focus on the role of rTMS and microglia in three major neurodegenerative conditions.

4.1. Alzheimer's disease

AD is characterized by pronounced microgliosis and chronic neuroinflammation, which occur alongside the accumulation of extracellular A β -plaques and the formation of intraneuronal neurofibrillary tangles [68]. These pathological features drive microglia into a chronically reactive state, leading them to adopt a disease-associated molecular profile [69]. Multiple rTMS protocols, applied over several days, have been shown to increase plasticity markers and acetylcholinesterase activity [70], reduce or slow the A β accumulation, and promote long-term cognitive improvements in AD animal models [71–75]. HF-rTMS (20–25 Hz; 400 and 1000 pulses) administered to 5xFAD and 3xTg-AD mouse models for 14 to 28 consecutive days reversed alterations in synaptic plasticity in hippocampal neurons, enhanced the expression of synaptic proteins [76,77], and prevented the decline of long-term memory performance [73]. Notably, rTMS has been shown to reduce both A β deposition and microglial activation in the neocortex and hippocampus, as reflected by decreased expression of the microglial marker Iba1 and the lysosomal protein CD68, two key indicators of inflammatory microglial state [73,77,78]. This reduction in microglial activation is associated with a decrease in the release of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , as well as a reduction in reactive oxygen species production. These protective anti-inflammatory effects are mediated, at least in part, through the activation of the PI3K/Akt signaling pathway [76,77]. The long-term effect of iTBS was tested on six-month-old APP/PS1 mice treated for 30 consecutive days (1200 pulses each session). In two rat models where an AD-like phenotype was induced by injection of streptozotocin [79] or trimethyltin [80], 15 days of iTBS600 (two sessions per day) improved cognitive impairments and reduced behavioral symptoms such as hyperactivity, anxiety, and tremor, likely mediated via PI3K/Akt/mTOR signaling pathway [80]. Two-week iTBS600 ameliorated mild reactive microgliosis in different regions of the hippocampus and neocortex [79], reduced pro-inflammatory IL-1 β cytokine, and increased anti-inflammatory cytokine IL-10 [80].

In summary, multi-day rTMS protocols lead to improvements in several aspects of AD progression, including the associated microgliosis. Yet, it remains unclear whether microglia actively contribute to these effects or if their reduced activation is simply a downstream consequence of altered neural excitability, activity, and a lower A β burden. Recent studies have investigated the effects of rTMS on individuals with mild cognitive impairment and AD [81,82] providing compelling evidence of its potential benefits for AD patients. However, several key questions remain unanswered, particularly regarding the underlying mechanisms of rTMS and the optimal strategies for maximizing its therapeutic potential in humans. The application of rTMS in AD faces significant challenges. In animal models, substantial variability in A β plaque burden persists even within identical experimental cohorts, while in clinical settings, determining the optimal timing and stimulation parameters for intervention throughout disease progression remains a major hurdle.

4.2. Parkinson's disease

Recent research has employed rTMS to explore the mechanisms underlying its therapeutic effects observed in PD patients [83]. PD is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as tremors, rigidity, bradykinesia, and postural instability, as

well as non-motor symptoms like cognitive impairment and mood disorders [84,85]. Microglia play a dual role in PD, exhibiting both neuroprotective and neurotoxic effects [86]. In response to alpha-synuclein aggregates and dying dopaminergic neurons, microglia become activated and produce pro-inflammatory cytokines and reactive oxygen species, which can contribute to disease progression [87]. Although the initial activation of microglia aids in clearing cellular debris and promoting tissue repair, chronic activation can exacerbate neurodegeneration by persistently releasing inflammatory cytokines [88]. Although studies have demonstrated the therapeutic potential of rTMS in animal models for PD, few have specifically investigated its effects on microglia.

Cacace et al. (2017) applied a single iTBS (50Hz; 300 pulses) intervention in a 6-hydroxydopamine (6-OHDA) lesioned rat model and analyzed its short-term effect after 20 and 80 min [89]. Interestingly, acute iTBS (50 Hz; 600 pulses) significantly restored both LTD and LTP in the striatum of 6-OHDA lesioned rats 80 min post-intervention, with only partial restoration after 20 min. This indicated a successful recovery of corticostriatal plasticity, along with improved motor performance [89]. Additionally, iTBS reduced Iba-1 immunoreactivity 20 min post-treatment, with the strongest effect observed at 80 min, confirming that rTMS can modulate microglia activation and influence neuronal network activity in PD. Transcript screening for therapeutic targets in unilaterally 6-OHDA-lesioned rats identified Clec7a as a gene significantly overexpressed in the substantia nigra and striatum of PD rats with dopaminergic neuron damage. Clec7a, mainly expressed in microglia, acts as a pattern recognition receptor involved in neuroinflammation and it is significantly down-regulated upon rTMS stimulation [90]. Inhibition of Clec7a induced a shift in microglial polarization from a pro-inflammatory to an anti-inflammatory phenotype contributing to its neuroprotective effects in PD. Therefore, Clec7a has been proposed as a molecular target for rTMS to mitigate motor deficits and dopamine injury in PD [90]. Despite the well-established role of microglia in PD pathophysiology, research on their specific involvement following rTMS intervention remains notably limited. A major translational challenge in applying rTMS for PD treatment in humans is the difficulty of effectively stimulating the deep brain regions most affected by the disease. In rodent models, electromagnetic fields can easily reach the basal ganglia and mesencephalon, whereas in humans, rTMS typically affects tissue only 2–4 cm beneath the cortical surface; depending on the coil type and stimulation intensity deeper regions may also be reached [91–93]. Although neuronal excitation can propagate along stimulated axonal pathways, including secondary activation in connected regions both anterogradely and retrogradely, the differential responsiveness of microglia within the primary electromagnetic field versus those in remotely connected brain areas remains poorly understood and requires further and systematic investigation.

4.3. Ischemic strokes

Rodent models of ischemic stroke, induced by transient or permanent cerebral vessel occlusion, have demonstrated promising outcomes for rTMS-mediated functional recovery. In the acute phase, microglia rapidly activate in response to tissue damage from oxygen deprivation, undergoing morphological changes and migrate to the injury site. There, they play a complex role in neuronal survival and recovery by producing both pro- and anti-inflammatory mediators, which can either support or impede recovery. Beyond their inflammatory roles, activated microglia influence neuronal excitability, modulate synaptic function, and contribute to angiogenesis and tissue repair [94]. Various rTMS protocols applied after Middle Cerebral Artery Occlusion (MCAO) in rats have demonstrated significant benefits, including reduced infarct volume, improved neurological scores [95], increased BDNF expression, and enhanced neuroplasticity in the peri-infarct cortex, promoting functional recovery [96]. Additionally, rTMS has been shown to enhance neurogenesis and cell migration [97–99].

A study by J. Luo et al. (2022) compared short-term (seven days) and long-term (28 days) HF-rTMS treatment using a 10 Hz protocol and 1200 pulses per session [98]. While microglial proliferation remained constant in both, long-term rTMS significantly reduced microglial inflammatory polarization and the release of pro-inflammatory cytokines IL-1 β and TNF- α , attributed to inhibition of the NF- κ B/STAT6 pathway. Notably, these anti-inflammatory effects were absent in the short-term (seven-day) treatment group, highlighting the importance of treatment duration.

A recent study using a 10 Hz rTMS protocol (600 pulses) for seven days post-MCAO found that rTMS-treated rats exhibited increased expression of the anti-inflammatory marker CD206 and reduced iNOS expression [100], indicating a shift towards an anti-inflammatory microglial phenotype. *In vitro* experiments with BV2 microglial cells subjected to oxygen-glucose deprivation and reoxygenation (OGD/R) confirmed these findings, as rTMS enhanced CD206 and IL-10 expression while reducing iNOS and TNF- α levels. Conditioned medium from rTMS-treated cells decreased neuronal cell death in cultures, demonstrating the direct neuroprotective effects of rTMS-induced microglia modulation. Further investigation revealed that the microRNA let-7b-5p, upregulated in the peri-infarct region after rTMS, regulates the HMGA2/NF- κ B pathway in microglia [100]. Recent findings also demonstrate that IL-10 can restore rTMS-induced synaptic plasticity by reducing pro-inflammatory cytokines in inflamed tissues, suggesting its critical role in rTMS-induced neuroprotection and providing a biological basis for the diagnostic use of rTMS in the context of brain inflammation [101].

Importantly, rTMS has been shown to significantly reduce the production of pro-inflammatory cytokines IL-1 β , TNF- α , IFN- γ , and TGF- β [102], while promoting a shift in microglia toward a more physiological surveillance state [97,103,104]. This effect is mediated by suppression of pro-inflammatory signaling in the infarcted area via the TLR4/NF κ B/NLRP3 signaling pathway [103]. However, it remains unclear whether these effects stem from a direct influence of the electromagnetic field on microglia, indirect modulation via neurons, astrocytes, oligodendrocytes, or the vasculature, or a combination of these mechanisms. Collectively, these findings underscore the potential of rTMS as a powerful therapeutic tool for ischemic stroke, acting through multiple mechanisms, including neuroprotection, neuroplasticity enhancement, and modulation of neuroinflammatory responses. The ability of rTMS to shape microglial phenotypes and signaling pathways opens promising avenues for targeted interventions in stroke recovery, extending beyond its role in synaptic plasticity.

5. Context-dependent pro-inflammatory effects of rTMS

While rTMS has demonstrated efficacy in reducing microglia-mediated inflammation in major neurodegenerative diseases, a study by Muri et al. (2020) revealed unexpected effects in a pneumococcal meningitis model [105]. Using both *in vivo* and *in vitro* approaches with *Streptococcus pneumoniae*-induced inflammation, they found that both cTBS600 and iTBS600 on two consecutive days promoted an inflammatory microglial phenotype, resulting in reduced neurogenesis, neuroplasticity, and regenerative processes.

Specifically, cTBS600 enhanced the release of pro-inflammatory cytokines *in vitro*. In the context of pneumococcal meningitis, cTBS exacerbated neuroinflammation, increasing the expression of microglia and astrocyte activation markers, immune response genes and pro-inflammatory mediators. Conversely, there was a downregulation of genes related to neurogenesis, axonogenesis, and the regulation of excitatory post-synaptic potential. These findings contrast with the anti-inflammatory effects of rTMS in neurodegenerative disease models, suggesting that its impact on neuroinflammation and brain plasticity is highly context-dependent. It is worth noting that in our *in vitro* study using bacterial lipopolysaccharide (LPS) to induce inflammation, 10 Hz rTMS stimulation did not exhibit any cytotoxic effects, as evidenced by

propidium iodide staining [101]. The studies underscore the complexity of rTMS effects, emphasizing the need for tailored neuromodulation strategies based on disease-specific pathology. A careful evaluation of rTMS protocols and their impact on microglia across different conditions is crucial for gaining a deeper understanding of its mechanisms of action, optimizing therapeutic outcomes, and minimize potential adverse effects.

6. rTMS-induced microglial modulation: effects on neurogenesis, neuroprotection, and phagocytic activity

Direct evidence for microglia-mediated neuroprotective effects of rTMS remains limited. This gap exists because the interaction between rTMS interventions and microglia depletion or impairment has not yet been thoroughly investigated under pathological conditions. However, recent studies have started to address this limitation, providing new insights into the role of microglia in rTMS-induced neuroprotection.

Microglial pyroptosis is an inflammatory form of programmed cell death primarily triggered by the activation of the NLRP3 inflammasome [106,107]. This process is characterized by the rapid rupture of the cell membrane and the release of cellular contents. When microglia undergo pyroptosis, they release a cascade of pro-inflammatory cytokines, as well as danger-associated molecules. This release can activate neighboring microglia and other cells such as astrocytes and infiltrating immune cells, potentially initiating a self-perpetuating cycle of inflammation. In the context of neurodegenerative conditions, this exacerbated neuro-inflammatory response contributes to secondary damage, further compromising neuronal health and function [107]. Qin et al. (2024) investigated the mechanism of rTMS by examining hippocampal neurogenesis and neuroinflammation in mice with radiation-induced brain injury [108]. They found that applying two daily sessions of rTMS (10 Hz; 1000 pulses) repeated 28 consecutive days after radiation exposure enhanced hippocampal neurogenesis while reducing NLRP3 inflammasome-induced microglial pyroptosis and the subsequent release of proinflammatory cytokines [108]. The study further revealed that rTMS increased hippocampal BDNF levels, implicating the BDNF pathway in the observed anti-pyroptotic effect. Notably, blocking the BDNF pathway led to an increase of the pyroptotic marker Gasdermin D+ in Iba1-expressing cells, indicating elevated microglial pyroptosis. This study demonstrated a more direct impact of rTMS on microglia, which can influence downstream neuronal function.

Mice subjected to MCAO received intermittent iTBS600 treatment over the ipsilesional hemisphere during the acute stage [103]. The treatment, administered twice daily for seven consecutive days, resulted in significant improvements in motor behavioral deficits and inhibited cerebral ischemia-induced neuronal pyroptosis in the peri-infarct area. The neuroprotective effects and functional improvements observed after multi-day iTBS600 were closely associated with the modulation of microglial activation. Indeed, when microglia were depleted using the CSF1R inhibitor PLX3397, the motor functional improvements typically seen after iTBS treatment were eliminated, thus underscoring the crucial role of microglia in mediating the beneficial effects of iTBS [103].

In animal models of spinal cord injury (SCI), the accumulation of myelin debris exacerbates neuroinflammation by increasing the production of inflammatory molecules, reactive oxygen species and nitric oxide [109,110]. Post-SCI, activated microglia are essential for clearing this myelin debris through phagocytosis, a process crucial for mitigating neuroinflammation and promoting functional recovery. Rats with C2 spinal cord hemisection, a condition causing diaphragmatic paralysis, exhibited significant improvement following multi-day HF-rTMS (10 Hz; 900 pulses). Treatment for 7 days, 1 month, or 2 months led to amelioration of respiratory dysfunction and a reduction in post-traumatic inflammatory responses, as indicated by decreased expression of Iba1 and CD68 in the C1–C3 spinal cord segments [111]. A recent study by Zhai et al. (2024) examined the impact of trans-spinal magnetic stimulation, a technique involving the placement of a

magnetic stimulator coil directly on the injured spinal cord [112]. The study found that this method significantly improved functional recovery in SCI rats by enhancing microglia-mediated phagocytosis of myelin debris. This beneficial effect was mediated via the Low-density lipoprotein receptor-related protein 1 (LRP-1) pathway.

7. Conclusions, challenges and future directions

Microglia are increasingly recognized as a key mediators of rTMS-induced neuroplasticity and therapeutic effects. This review highlights animal studies examining microglial morphology, functional states, and behavioral outcomes in response to rTMS protocols across various neurological conditions. The evidence suggests that rTMS can modulate both acute and long-term microglial response, shifting them from a resting state into a plasticity promoting state or from a pathological (pro-inflammatory) to more physiological surveillance state. These transitions appear to play a crucial role in neuroprotection, neuroplasticity and functional recovery (Fig. 2B). However, fundamental questions remain regarding the precise mechanisms by which rTMS influences microglial function, particularly whether these effects are due to a direct electromagnetic influence on microglia or indirect modulation via neurons, astrocytes, oligodendrocytes, vasculature or a combination of these factors.

A critical gap in current research is the lack of causal evidence linking microglial changes to rTMS-induced neuroplastic effects, particularly during prolonged stimulation. While studies have shown that microglia can influence neuronal properties following a single 10 Hz rTMS intervention [24], the effects of multi-day rTMS on synaptic plasticity and the specific role of microglia remain entirely unknown, leaving open questions in our understanding of its long-term consequences. Selective microglia manipulation, such as depletion or functional alteration, is necessary to determine whether microglia are primary mediators of rTMS effects or merely responding to a broader network change. Moreover, while some studies indicate that rTMS benefits can persist for months post-treatment [48], little is known about the stability of microglial changes and their long-term impact on synaptic plasticity.

The sustainability and safety of repeated rTMS sessions introduce further complexities, particularly concerning microglial involvement. While rTMS-induced neuroplasticity can be long-lasting, the durability of these effects varies among individuals, with some requiring maintenance sessions to sustain therapeutic benefits [113]. A crucial concern is whether prolonged and repeated stimulation induces maladaptive microglial responses, such as sustained reactivity, persistent inflammatory signaling, or disruptions in synaptic pruning and circuit remodeling. Such chronic changes could impact treatment efficacy and potentially affect brain homeostasis. To address this, we are currently investigating how prolonged iTBS affects neuronal and microglial activity. Specifically, our research focuses on whether prolonged stimulation induces shifts from microglia-mediated Hebbian plasticity to homeostatic plasticity mechanisms.

Individual variability in microglial responses further underscores the need for personalized rTMS interventions, particularly in neurodegenerative conditions where microglia play a fundamental role in disease progression. A standardized approach ensures experimental consistency, yet truly effective rTMS therapy may require personalization, taking into account factors such as sex, age, targeted brain regions, disease condition, medication use, and the presence of pathological markers. Bioinformatic simulations and computational modeling hold promise for optimizing individualized rTMS protocols, enhancing therapeutic efficacy while minimizing adverse effects. The identification of reliable biomarkers could inform these modeling approaches, improving precision in predicting and tailoring rTMS effects. However, currently validated biomarkers for tracking or predicting rTMS outcomes in both health and disease are lacking, limiting our ability to account for inter- and intra-individual variability in both animal and human studies.

Translocator Protein Positron Emission Tomography (TSPO-PET) has been used to assess microglial activation in the intact brain and represents a promise as a tool for identifying biomarkers to track the short- and long-term effects of rTMS on microglia [114]. Nevertheless, studies in animal models remain essential for biomarker discovery, ultimately paving the way for more personalized and effective rTMS protocols.

In preclinical models of neurodegenerative diseases rTMS has demonstrated promising effects in reducing neuroinflammation and enhancing cognitive and motor functions. These outcomes are closely linked to the modulation of microglial phenotypes and the suppression of pro-inflammatory cytokine release. Recent studies have expanded our understanding on rTMS-microglia interactions, revealing novel mechanisms such as modulation of microglial pyroptosis, enhancement of phagocytic activity, and regulation of neurogenesis [103,108,112]. However, a significant limitation in existing research is the narrow range of stimulation parameters investigated and the limited number of studies examining whether microglial depletion or dysfunction negates the benefits of rTMS. Given the growing evidence of microglia-neuron cross-talk [55,59,115], future studies should investigate whether rTMS exerts its effects by directly modulating microglia or through downstream neuronal changes.

Advances in single-cell RNA sequencing and spatial omics have revealed substantial spatial and temporal heterogeneity in microglial populations, exposing limitations of the conventional M1/M2 classification. Microglia exhibit diverse functional states depending on their environment, brain region, and disease context [69,116–118]. For example, in AD mouse models, distinct microglial subtypes are present, including reactive plaque-associated microglia and more ramified, less reactive microglia further from A β -plaques (Fig. 1B; [119]). Understanding this heterogeneity is crucial for rTMS-based therapies, as microglia may exert differential effects depending on their state.

Microglia diversity extends beyond disease conditions to include regional, age-related and sex-based differences [120,121]. Microglia density is higher in the forebrain than the hindbrain and more prevalent in gray matter than white matter [122]. Morphologically, microglia range from compact, short-process cells to highly ramified forms, depending on their activation state, which may influence their direct or indirect response to rTMS. Additionally, microglial marker expression, activation profiles, and synaptic pruning capabilities vary significantly across different brain areas [123,124]. These variations are further influenced by age and sex, with male and female microglia exhibiting distinct phagocytic, migratory, and inflammatory responses [125–127]. These differences may underlie the heterogeneous responses to rTMS across individuals and must be accounted for in both experimental designs and translational applications.

The translational relevance of rTMS findings from animal models to humans is another critical challenge. Although fundamental microglial genes are conserved between species (e.g., CX3CR1, P2RY12, TMEM119, TREM2, IRF8, PU.1 and SALL2) [128] cross-species comparisons reveal significant differences in gene expression, immune responses, and microglial aging patterns [129,130]. For example, human microglia exhibit lower TLR4 expression compared to rodents and demonstrate stronger inflammatory responses due to species-specific antigen presentation machinery [32]. These interspecies differences require cautious interpretation of preclinical findings and underscore the need for complementary models, such as human-induced pluripotent stem cell (iPSC)-derived microglia, brain organoids, and experiments in living human cortical slices from neurosurgical access material, to improve translational relevance.

Another major limitation in the field is the lack of standardization in rTMS parameters across studies. Variability in stimulation protocols, duration, and coil types (as summarized in Table 1) complicates direct comparisons and hinders reproducibility. A critical yet often overlooked factor is the induced electric field, which significantly impacts stimulation efficacy. Rather than being directly measured, these fields are typically estimated using finite element modeling and other

Table 1
rTMS protocols and magnetic coils used in the studies described in this review.

Studies	Stimulation & experiment duration	Assessment time post-stimulation	Frequency	Intensity	Magnetic coil/machine	Research Model	Condition	Microglia responses after stimulation
[38] Eichler et al., 2023	rTMS; 1 time	2–4 h	10 Hz; 900 pulses	50 % MSO; estimated max. electric field: 27 V/m.	Double AirFilm 70 mm eight-Coil/Rapid2 stimulator (Magstim Ltd, UK)	Mouse entorhino-hippocampal slice cultures	Health; microglia depletion	No changes in morphology and dynamics; no inflammatory response; activity-dependent release of plasticity-promoting microglial cytokines
[38] Eichler et al., 2023	rTMS; 1 time	2–4 h	10 Hz; 900 pulses	60 % MSO (90 % motor threshold)	Double AirFilm 70 mm eight-Coil/Rapid2 stimulator (Magstim Ltd, UK)	C57BL/6J mice (8week old)	Health; microglia depletion	No rTMS-induced changes in microglia morphology
[66] Zorzo et al., 2019	rTMS; 3 consecutive days	90 min after last stimulation	100Hz; 3000 pulses/min	330 mT	Custom built round coil	young Wistar rats	Health	No effect on microglia numbers
[67] Liebetanz et al., 2003	rTMS; 5 consecutive days	48 h after last stimulation	1 Hz; 1000 pulses	7 T (115 % motor threshold)	7–32 mm round commercial coil	Wistar rats	Health	No significant changes in microglia numbers and activation; absence of ED1-expressing phagocytting microglia
[76] Cao et al., 2022	rTMS; 21 consecutive days	Not specified	25 Hz; 10 trains of 100 pulses each (tot. 1000 pulses). Intertrain interval of 25 s.	60 % MSO	eight- Coil/ Rapid2 stimulator (Magstim Ltd, UK)	3xTg-AD model mice	AD	Reduced neuroinflammation; increased proliferation of microglia in hippocampal DG region; reduced activation of microglia in DG; decreased levels of pro-inflammatory cytokines
[78] Huang et al., 2023	iTBS; 30 consecutive days	2 months after iTBS (9 months old)	50 Hz, 1200 pulses	32–36 % MSO (80 % motor threshold); 1.92–2.16T	60 mm coil/CCY-I magnetic stimulator (Yiruide, Wuhan, China)	APP/PS1 (6 month old)	AD	Decreased number and activation of microglia
[77] Li et al., 2021	rTMS; 14 consecutive days	Not specified	20 Hz; 400 pulses	90 % motor threshold	10–24.5 mm Eight-coil/ Rapid2 stimulator (Magstim Ltd, UK)	5xFAD (2 month old)	AD	Decreased microglia activation; decreased levels of pro-inflammatory cytokines
[73] Lin et al., 2021	rTMS; 14 consecutive days	Not specified	20 Hz; 4000 burst trains	1.38 T	6.5 cm round coil/stimulator CCY-II, Wuhan Yiruide Medical Equipment	5xFAD (4–5 month old)	AD	Decreased activation, density and soma size of microglia
[79] Stanojevic et al., 2022	iTBS; two 5-days sessions with two-day break in between	6 days after last stimulation	50 Hz, 600 pulses	33 % MSO (below motor threshold)	25 mm eight-Coil/Rapid2 stimulator (Magstim Ltd, UK)	Wistar rats (10 week old)	AD	Ameliorated mild reactive microgliosis; changed microglia morphology towards resting state
[102] Caglayan et al., 2019	rTMS; one time and 28 consecutive days	24 h or 10 days after last stimulation	1 Hz and 20 Hz	26 % MSO	34–94 mm eight-Coil/stimulator Neurosoft, Avm Saglik	Balb/c mice (10–12 week old)-MCAO model	Ischemic stroke	HF-rTMS: decreased microglia number and activation; slightly decreased microglia proliferation
[100] Hong et al., 2022	rTMS; 7 consecutive days	Not specified	10 Hz, 600 pulses	1.9 T	20 mm C-100 circular Coil/stimulator MagPro X 100 with Magoption, Tonica, DK	Sprague-Dawley rats -MCAO model	Ischemic stroke	Inhibition of ischemia-reperfusion induced M1 microglia polarization; increased let-7b-5p expression in microglia.
[100] Hong et al., 2022	rTMS; 2 consecutive days	Not specified	10 Hz, 600 pulses	1.9 T	20 mm C-100 circular Coil/stimulator MagPro X 100 with Magoption, Tonica, DK	BV2 cell line	OGD/R	Inhibition of OGD/R-induced M1 polarization of microglia; increase of let-7b-5p expression in microglia; lower level of TNF- α and increased IL-10 concentration in culture medium.
[98] Luo J et al., 2022	rTMS; 7 or 28 consecutive days	After 7th or 28th day of rTMS	10 Hz, 1200 pulses	4.2 T	24–47 mm eight-Coil/stimulator MagPro X100	Wistar rats-MCAO model	Ischemic stroke	Short/long-term treatment: anti-inflammatory polarization

(continued on next page)

Table 1 (continued)

Studies	Stimulation & experiment duration	Assessment time post-stimulation	Frequency	Intensity	Magnetic coil/machine	Research Model	Condition	Microglia responses after stimulation
[103] Luo L et al., 2022	iTBS; twice/day, 7 continuous days	After 7th day of iTBS	50 Hz, 600 pulses	20–30 % MSO	magnetic stimulators (The MagVenture Company 6.5 mm round-Coil/stimulator CCY-II, Wuhan Yiruide Medical Equipment	Adult male C57BL/6 J mice (20–25 g)	Ischemic stroke	of microglia; Long-term treatment: reduced inflammatory polarization of microglia Reduced pro-inflammatory M1 activation; enhanced anti-inflammatory M2 activation
[89] Cacace et al., 2017	iTBS; one time	20 or 80 min after stimulation	50 Hz, 300 pulses	30 % MSO	70 mm 8-shaped coil/Rapid2 stimulator (Magstim Ltd, UK)	Wistar rats (150–250g)-6-OHDA-lesioned model	PD	80 min post stimulation: reduces microglial activation
[108] Qin et al., 2024	rTMS; two sessions (2 min interval) for 32 consecutive days	Not specified	10 Hz, 500pulses	Not specified	Not specified	C57BL/6 mice (6–8 week-old)	RIBI	Changes in microglia morphology; mitigates pyroptosis in microglia.
[111] Michel-Flutot et al., 2022	rTMS for 7 consecutive days, 1 month or 2 months (once a day, 5 days per week) applied 7days post-injury.	After last stimulation	10 Hz, 900 pulses	50 % MSO	8-shaped coil (Cool-B65)/MAGPRO R30 (Magventure, Farum, Denmark)	Adult Sprague Dawley male rats (350–450 g)	SCI	Decrease expression of Iba1 and CD68 reactive microglia markers.
[112] Zhai et al., 2024	rTSMS; 11 consecutive days	after last stimulation or 14 days after last stimulation	20 Hz, 2400 pulses	0.35 T	2.5–5 cm circular Coil/stimulator CCY-IA, Wuhan, Hubei, China)	Sprague-Dawley rats (200–230 g, 9–11 Week-old)	SCI	Inhibits neuroinflammation; Increases microglial phagocytosis
[105] Muri et al., 2020	cTBS; iTBS; 2 consecutive days (4 stimulations/day)	24 h after last stimulation	cTBS: 30Hz, 600pulses. iTBS: 50 Hz, 600 pulses (4800 pulses tot.)	16 % MSO	Cool-40 rat coil (MagVenture, Denmark)	Wistar rats (infant)	PM	Upregulation of markers for reactive microglia; polarization of microglia to inflammatory phenotype.

Abbreviations. AD: Alzheimer's disease; PD: Parkinson's disease; OGD/R: oxygen-glucose deprivation and reoxygenation; RIBI: radiation-induced brain injury; SCI: spinal cord injury; PM: pneumococcal meningitis; MSO: maximum stimulator output.

computational tools [91]. To enhance translational potential, they should be carefully controlled, accurately reported, and integrated into experimental designs.

Moving forward, research on rTMS and microglia should focus on: (1) Expanding the range of examined parameters to refine our understanding of how different rTMS protocols influence microglia activity; (2) Conducting studies with selective microglial depletion or impairment to establish causal links between microglial activation and rTMS-induced neuroplasticity and neuroprotection; (3) Investigating both immediate and long-term effects of rTMS, with a particular focus on its sustained impact on microglial function and overall brain health (including potential adverse effects); (4) Considering microglial heterogeneity in terms of spatial distribution, age, sex, and disease-specific states; (5) Exploring interactions with other glial cells, such as astrocytes and oligodendrocytes [131–134], and the potential role of the blood-brain-barrier in activity-dependent glia-neuron interactions; (6) Identifying and validating (microglial) biomarkers to predict and monitor rTMS efficacy; (7) Integrating these insights into multi-scale modeling approaches to enhance rTMS outcomes and enable personalized interventions.

As this field develops, a deeper understanding of rTMS-microglia interactions may pave the way for optimizing stimulation protocols tailored to specific neuropsychiatric conditions. However, caution must be exercised in interpreting current findings, and more robust, systematic studies are needed to fully elucidate the complex interplay between rTMS, microglia, and neurons in both health and disease.

CRediT authorship contribution statement

Paolo d'Errico: Writing – review & editing, Writing – original draft, Conceptualization. **Iris Frühholz:** Writing – review & editing. **Melanie Meyer-Luehmann:** Writing – review & editing, Funding acquisition. **Andreas Vlachos:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

All experimental procedures were performed according to German animal welfare legislation and approved by the competent authority (Regierungspräsidium Freiburg, G-22/105), appropriate animal welfare committee, and the animal welfare officer of the University of Freiburg, Faculty of Medicine (X-22/12B). Human tissue was obtained from the local biobank of the Department for Neurosurgery at the Faculty of Medicine. Experiments were approved by the Local Ethics Committee, University of Freiburg (AZ 24-1230-S1). Patients gave their informed consent to use the neurosurgical resection material for research purposes.

Consent for publication

All authors have given their consent for the manuscript to be published.

Availability of data and materials

Not applicable.

Declaration of generative AI in scientific writing

During the preparation of this work the authors used ChatGPT/OpenAI exclusively to improve the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding sources

This work was supported by the Federal Ministry of Education and Research, Germany (BMBF, 01GQ2205A) and Deutsche Forschungsgemeinschaft (DFG, TRR 384/1 2024, – 514483642, B03; DFG, CRC/TRR 167/3 2025, – 259373024, B14).

Declaration of competing interest

The authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

We thank Dr. Elli-Anna Balta for providing the image of stained microglia in the human neocortex.

List of abbreviations

6-OHDA	6-hydroxydopamine
AD	Alzheimer's disease
A β	Amyloid- β
BDNF	Brain-Derived Neurotrophic Factor
HF-TMS	High-frequency transcranial magnetic stimulation
IL6	Interleukin 6
iTBS	Intermittent theta-burst stimulation
LF-TMS	Low-frequency transcranial magnetic stimulation
LRP-1	Low-density lipoprotein receptor-related protein 1
LTD	Long-term depression
LTP	Long-term potentiation
MCAO	Middle Cerebral Artery Occlusion
mPFC	Medial prefrontal cortex
OGD/R	Oxygen-glucose deprivation and reoxygenation
PD	Parkinson's disease
PM	Pneumococcal meningitis
RIBI	Radiation-induced brain injury
rTMS	Repetitive transcranial magnetic stimulation
SCI	Spinal cord injury
TNF α	Tumor Necrosis Factor α

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